MS07-P15 | STRUCTURAL INSIGHT IN PEPTIDYL SUBSTRATE BINDING TO CYSTEINE CATHEPSINS

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We are trying to understand how cysteine cathepsins select their endogenous substrates. Analysis of proteomic study of the cell lysate, which was enriched with selected cathepsins, suggested representative peptides as a model of protein substrates based on cathepsin's specific cleavages. Using a structural approach we attempted to validate the peptide model with the crystal structures of active-site mutant human cathepsin V in complex with those peptides. The first generation peptides were designed to explore possible cooperative effects of amino acids binding into S1 and S2' subsites of the enzyme. The second generation peptides were hexapeptides selected from the proteomic data. We observed electron density of mainly cleaved or shifted peptides at the active site, possibly due to interactions of their charged termini. The analysis of the third generation peptides of various lengths, which have N- and C- termini protection, is ongoing.